Signalling thresholds and negative B-cell selection in acute lymphoblastic leukaemia.

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Public Summary:
B cells are selected for an intermediate level of B-cell antigen receptor (BCR) signalling strength: attenuation below minimum (for example, non-functional BCR) or hyperactivation above maximum (for example, self-reactive BCR) thresholds of signalling strength causes negative selection. In approximately 25% of cases, acute lymphoblastic leukaemia (ALL) cells carry the oncogenic BCR-ABL1 tyrosine kinase (Philadelphia chromosome positive), which mimics constitutively active pre-BCR signalling. Current therapeutic approaches are largely focused on the development of more potent tyrosine kinase inhibitors to suppress oncogenic signalling below a minimum threshold for survival. We tested the hypothesis that targeted hyperactivation--above a maximum threshold--will engage a deletional checkpoint for removal of self-reactive B cells and selectively kill ALL cells. Here we find, by testing various components of proximal pre-BCR signalling in mouse BCR-ABL1 cells, that an incremental increase of Syk tyrosine kinase activity was required and sufficient to induce cell death. Hyperactive Syk was functionally equivalent to acute activation of a self-reactive BCR on ALL cells. Despite oncogenic transformation, this basic mechanism of negative selection was still functional in ALL cells. Unlike normal pre-B cells, patient-derived ALL cells express the inhibitory receptors PECAM1, CD300A and LAIR1 at high levels. Genetic studies revealed that Pecam1, Cd300a and Lair1 are critical to calibrate oncogenic signalling strength through recruitment of the inhibitory phosphatases Ptpn6 (ref. 7) and Inpp5d (ref. 8). Using a novel small-molecule inhibitor of INPP5D (also known as SHIP1), we demonstrated that pharmacological hyperactivation of SYK and engagement of negative B-cell selection represents a promising new strategy to overcome drug resistance in human ALL.

Scientific Abstract:
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